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10/696,051	10/28/2003	Su Chen	034827-2601	5893

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EXAMINER	
WEISZ, DAVID G	
ART UNIT	PAPER NUMBER
1777	
MAIL DATE	DELIVERY MODE
12/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,051	CHEN, SU	
	Examiner	Art Unit	
	DAVID WEISZ	1777	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-13,15-17,30-32,34-41 and 43-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-13,15-17,30-32,34-41 and 43-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of remarks filed 10/12/10. Claims 2, 5, 14, 18-29, 33, and 42 are canceled, and claims 57-61 are new. Claims 1, 3-4, 6-13, 15-17, 30-32, 34-41, and 43-61 are pending and presented for examination.

Response to Amendment

2. In response to the amendments remarks filed 10/12/10, the examiner modifies the grounds for rejections. The 35 U.S.C. 112 second paragraph and 35 U.S.C. 103(a) rejections have been modified.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-4, 6-13, 15-17, 30-32, 34-41, and 43-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1, 9, 30 and 37, the claims disclose the addition of an unlabeled organic acid and measuring a unlabeled and labeled organic acid. Does the sample contain unlabeled and labeled organic acids? If so, which labeled organic acid is the focus of measurement? The specification, in paragraph [0007], discloses that a labeled internal standard is used to make adjustments to an unlabeled sample, to correct for loss during processing. The claims will be interpreted in that the sample contains only unlabeled organic acids and the internal standard is a similar or identical labeled organic acid. Thus it appears that the instant claims recite conventional usage of a labeled internal standard for quantifying an analyte of a similar nature by mass spectrometry.

5. Claims 7-8, 12-13, 31-32 and 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are drawn to a processing step, discussing enrichment and chemical modification. What does enrichment of the unlabeled organic acid actually entail? What sort of chemical modifications are taking place? These steps, as they are currently disclosed, are unclear and indefinite.

Claim Rejections - 35 USC § 103

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. **Claims 1, 3-4, 7-13, 15-16 and 57-59** are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (Journal of Lipid Research, 1988) (Peterson) in view of Nguyen et al. (US 2005/0070023) (Nguyen).

Regarding claims 1 and 3-4, Peterson discloses a method of labeling glycolic acid with an oxygen-18 atom at the carboxyl group (page 95, Col2). Further the reference discloses a method of sample analysis using gas and liquid chromatography mass spectroscopy (page 95, Col2). Peterson further discloses the sample to be biological (see "Glycolic acid, the substrate of photorespiration", Page 94, Left Column).

However, the reference does not specifically disclose the oxygen-18 labeled acid for use as an internal standard, nor the processing step of the sample.

Nguyen discloses a method of using stable isotope labeled internal standards in analysis of carboxylic acids (abstract). Using internal standards to quantify analytes samples in analysis is a well known practice in analytical chemistry, and Nguyen discloses that using oxygen-18 isotopes as internal standards in mass spectrometry is used for quantification of an analyte [0004]. Nguyen additionally discloses that the entire sample is processed via a chemical modification to convert the sample into a carboxylic acid ester prior to mass spectrometry [0025]. One having ordinary skill in the art would use the internal standard technique of Nguyen and the labeled glycolic acid of Peterson in a GC-MS or LC-MS analysis as it would allow one to quantify an unlabeled glycolic acid analyte by measuring structurally similar labeled internal standards. Further, one having ordinary skill in the art would be able to adjust an amount of unlabeled analyte, as is well known in the use of internal standards, using the method of Nguyen combined with Peterson.

Regarding claims 7-8, Peterson-Nguyen disclose all of the limitations as addressed above regarding the processing of the sample.

Regarding claim 9-11, Peterson-Nguyen disclose all of the limitations as addressed in claim 1 above. Further, the application of the above method to the other disclosed organic acids would have been obvious, as according to applicant's disclosure, they are patentably indistinct.

Further, it would have been obvious to apply the method to a sample containing more than one organic acid, as it would require only routine skill in the art to differentiate several species using mass spectroscopy.

Regarding claims 12-13 and 15-16, the references disclose all of the limitations as addressed above regarding processing and the specific type of mass spectrometry.

Regarding claims 57-59, the references disclose all of the limitations as set forth above. Further, the Peterson reference discloses that the sample is acidic, for at least part of the analysis process (see Page 95, Right Column, [^{18}O] Glycolic Acid).

8. **Claims 6, 17, 30-32, 34-41, 43-56 and 60-61** are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Nguyen, as applied to claims 1-4 and 7-16 above, further in view of Pang (HKMJ, 1996) (Pang).

Regarding claims 6 and 17, Peterson-Nguyen disclose all of claim limitations as applied to claim 1, above. However, the references do not specifically disclose that the method extends to analyzing urine.

Pang discloses a method of analyzing urine, and that accumulation of organic acids in urine is associated with many metabolic disorders (Page 269, "Organic Acid Analysis"). As the method of Peterson-Nguyen accurately determines the levels of carboxylic acids via GC-MS and LC-MS using oxygen-18 internal standards, one having ordinary skill in the art would naturally use the method in conjunction with the method of Pang, as it would increase accuracy of analysis.

Regarding claim 30, 36-37 and 45, Peterson-Nguyen-Pang disclose all of the claim limitations as referenced above. With this in mind, it would only require routine skill in the art to determine the accumulation of organic acids, as described by Pang, to diagnose the metabolic defect.

Regarding claims 31-32, 34-35, 40-41 and 43-44, Peterson-Nguyen-Pang disclose the processing and specific type of mass spectrometry already described above.

Regarding claims 38-39 and 54-56, Peterson-Nguyen-Pang already disclose that it would have been obvious to apply the method to a sample containing more than one organic acid.

Regarding claims 46-53, Peterson-Nguyen-Pang already disclose that application of the above method to the other disclosed organic acids would have been obvious, as according to applicant's disclosure, they are patentably indistinct.

Regarding claims 60-61, the references disclose all the limitations as set forth above. Further, the Peterson reference discloses that the sample is acidic, for at least part of the analysis process (see Page 95, Right Column, [^{18}O] Glycolic Acid).

Response to Arguments

9. Applicant's arguments with respect to claims 1, 3-4, 6-13, 15-17, 30-32, 34-41, and 43-61 have been considered but are moot in view of the new ground(s) of rejection. However, pertinent arguments will be addressed from Applicants' Remarks filed 10/12/10.

On page 10, it is stated that "only after the determination is performed that the practitioner can known with certainty whether the sample did or did not contain an unlabeled organic acid of interest". Further, it is stated that "it is not clear what is meant by 'conventional usage'". Further, it is stated that "Applicant agrees with the Examiner to the extent that the claims require the addition of a known amount of an oxygen-18-labeled organic acid, quantification of the amount of that labeled organic acid by mass spectrometry, and use of that quantified amount to infer the amount of unlabeled organic acid (if any) that is present in the sample". The phrase 'conventional usage' is merely the standard practice of using labeled internal standards for quantifying an analyte of similar nature by mass spectrometry that is well known to one having ordinary skill in the art. Further, while disclosure of the "...use of that quantified amount to infer the amount of unlabeled organic acid (if any) that is present in the sample" is present in applicants' arguments, it is not; however, clearly delineated in the claims. Instead, the claims recite "using the amount of oxygen-18 organic acid measured in step c) to adjust the amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample." This remains unclear to the examiner, and thus the claims remain rejected under 35 U.S.C. 112 second paragraph in Item 4 above.

On page 10, it is stated that "it is clear from the Specification and common usage in the art that "enrichment" refers to the act of concentrating an analyte and "chemical modification"

refers to subjecting a molecule to a chemical process such as derivatization. While the definition of enrichment does not escape the Examiner, the method of enrichment is absent from the claims. Further, as argued on page 10, a chemical modification refers to subjecting a molecule to a chemical process. As there are many chemical processes that may result in a chemical modification, it is unclear exactly what process has taken place, despite what is suggested in the specification, thus rendering the claims indefinite.

On page 11, it is argued that the requirement that the sample is a biological sample" renders the claims non-obvious over the cited prior art. Please refer to Item 7 above. Further, it is argued that there is nothing in the Peterson reference that suggests the glycolic acid is suitable for use as an internal standard with a biological sample. As the term "biological" is not defined by the applicant, examination of the claim necessitates the broadest reasonable interpretation of this limitation. Glycolic acid itself is a biological substance, as can be seen in Item 7 above.

On page 12, it is argued that Nguyen teaches away from using an isotopic label such as [^{18}O] under the circumstances when the labeled analyte is generated by a simple isotope exchange reaction such as that demonstrated by Peterson. The applicants cite Nguyen paragraphs [0005]-[0006]. Specifically "The ideal [internal standard], however, must not contain any labeled isotope that can be exchanged for the isotope under particular sample preparation conditions" and "Most often the synthesis of stable isotope internal standards is not simply an isotope exchange reaction. Easily exchangeable atoms are usually avoided to possible re-exchange during sample preparation steps". However, in the very same paragraph, it is disclosed that "The commonly used stable isotope labeled internal standard of an analyte is a chemical compound that has the same chemical structure as that of the analyte except that one or more substituent atoms are stable isotopes. Four commonly used stable isotopes are deuterium, carbon-13, nitrogen-15, and oxygen-18". Obviously, one having ordinary skill in the art would want to avoid labeled isotope exchange under particular conditions. These conditions are not defined in these sections, but would be defined by the one carrying out the sample preparation. Further, what is meant by "easily exchangeable" is subject to interpretation. The Nguyen reference is cited because it discloses the use of oxygen-18 as a commonly used stable isotope for use as an internal standard.

On pages 13-14, several examples from the specification are cited. However, it is not clear how these examples refute the obviousness of Peterson-Nguyen-Pang, but rather act as working examples. Much of what is disclosed in these examples is not specifically recited in the instant claims. Thus, while the claims are read in view of the specification, limitations from the specification are not read into the claims. While the prior art may or may not illustrate the findings of the examples from the specification, these findings are not specific limitations to the invention as currently claimed.

On page 15, it is stated that it is not obvious to use an acidic biological sample in view of Peterson. Please refer to Items 7 and 8 above.

On page 16, it is argued that claims 9 and 37 require the use of a seven-way internal standard solution not taught or suggested in the prior art. It is argued that the Examiner has failed to fully examine these claims, cite to any prior art, or provide any reasoning as to why these claims are obvious. Please refer to Item 7 above, addressing claims 9-11, also applicable to claim 37.

Thus, in view of the above response to arguments and rejections, all claims remain rejected.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID WEISZ whose telephone number is (571)270-7073. The examiner can normally be reached on Monday - Thursday, 7:30 a.m. - 5:00 p.m., EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

12/17/2010

/Yelena G. Gakh/
Primary Examiner, Art Unit 1777

/D. W./
Examiner, Art Unit 1777